PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/025604	02.09.2004	05.09.2003

International Patent Classification (IPC) or both national classification and IPC
C07K16/28, C12N15/68, C12N5/10, A61K39/395, C12N15/13, C07K14/60

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Ulbrecht, M

Telephone No. +49 89 2399-7710

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/025604

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 25-28 (partially); 37,38 (IA)

because:

☒ the said international application, or the said claims Nos. 37,38 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 25-28 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-38,40
	No:	Claims	39
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-40
Industrial applicability (IA)	Yes:	Claims	1-36,39,40
	No:	Claims	

2. Citations and explanations

see separate sheet

Re item III:

1. Claim 25 refers to nucleic acids encoding an antibody ia. as defined by claims 1-3. These claims, however, only define the antibody in terms of functional features. The nucleic acid encoding the antibodies according to claims 1-3 cannot be determined and is therefore unclear to such an extend as to render a meaningful search thereof impossible (Art. 6 PCT). Consequently, claim 25 has only been searched insofar as the antibody is defined by structural features, namely as in claims 4-14.

1.2 The same applies to claims 26-28.

2. Claims 37 and 38 relate to subject-matter considered by this Authority to be covered by the provisions of R. 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Re item V:

1. Reference is made to the following documents:

D1: ARIYASU H ET AL: "Stomach is a major source of circulating ghrelin, and feeding state determines plasma ghrelin-like immunoreactivity levels in humans" ENDOCRINOLOGY, BALTIMORE, MD, US, vol. 86, no. 10, October 2001 (2001-10), pages 4753-4758

D2: EP-A-1 197 496 (KANGAWA, KENJI) 17 April 2002 (2002-04-17)

D3: WO 01/87335 A (ELI LILLY AND COMPANY; BRYANT, HENRY, UHLMAN; HEIMAN, MARK, LOUIS) 22 November 2001 (2001-11-22)

D4: MURAKAMI N ET AL: "Role for central ghrelin in food intake and secretion profile of stomach ghrelin in rats" JOURNAL OF ENDOCRINOLOGY, BRISTOL, GB, vol. 174, no. 2, August 2002 (2002-08), pages 283-288

D5: HOSODA HIROSHI ET AL: "Ghrelin and des-acyl ghrelin: Two major forms of rat ghrelin peptide in gastrointestinal tissue" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 279, no. 3, 29 December 2000 (2000-12-29), pages 909-913

D6: HOLT L J ET AL: "Domain antibodies: proteins for therapy" TRENDS IN BIOTECHNOLOGY, ELSEVIER PUBLICATIONS, CAMBRIDGE, GB, vol. 21, no. 11, November 2003 (2003-11), pages 484-490

2. *Novelty (Art. 33(2) PCT):*

2.1 The only technical feature characterising the kit according to claim 39 which is considered an entity (cf infra, item 5.4) is the proposed antibody. D1 (p. 4754, c. 2, para. 1), D2 (Example 16; claim 46), D3 (claims 1, 7 and 17), D4 (abstract) and D5 (p. 909, c.2, para. 3) disclose antibodies against ghrelin that are considered to neutralise ghrelin activity. Thus, the subject-matter of claim 39 lacks novelty over any of D1-D5.

2.2 The subject-matter of claims 1-38 and 40 is novel as the combination of features suggested by any of these claims is not disclosed in the prior art.

3. *Inventive step (Art. 33(3) PCT):*

3.1 D1 discloses a polyclonal antibody against the carboxy-terminal amino acids 13-28 of human ghrelin (p. 4754, c. 2, para. 1). The subject-matter of claim 1 differs therefrom in that the antibody is monoclonal and that the epitope is localised to amino acids 4-20. Generation of monoclonal antibodies is a matter of the skilled person's routine experimentation and the choice of epitope suggested by claim 1 is arbitrary as it is not associated with any technical effect not achieved by an epitope located between amino acids 13-28. Hence, claim 1 is considered not inventive.

3.2 For similar considerations also claims 2, 3, 29, 30 and 40 are considered not inventive.

3.3 D1 discloses a RIA determining acetylated and des-acyl human ghrelin (p. 4754, c. 2, para. 1). Claim 36 is distinguished from D1 only by the antibody used. Therefore, the considerations under 3.1 also apply to this claim.

3.4 D4 discloses a method of treating obesity and related disorders using a neutralising

antibody against ghrelin (claims 1, 7 and 13-16). The subject-matter of claim 37 is distinguished from D4 by the antibody used. For the considerations under 3.1, the antibody, however, is not considered to establish an inventive step.

3.5 The additional features suggested by claim 38 are disclosed in D4 (supra) and hence do not involve an inventive step.

3.6 Claims 4-14 are considered an arbitrary selection of anti-hGhrelin antibodies which do not produce any unforeseeable technical effect and which for the reasons given under 3.1 do not establish an inventive step.

3.7 The same considerations also apply to claims 25-28 and 33-35 which refer to products obtainable by routine experimentation or routinely applied methods which per se do not produce any unforeseeable technical effect and which, as the antibody is considered not inventive, do not involve an inventive step.

3.8 The additional features suggested by claims 15-24, 31 and 32 refer to modifications of the non-inventive antibody obtainable by routine experimentation which do not produce any unforeseeable technical effects and which therefore do not establish an inventive step.

4. *Industrial applicability (Art. 33(4) PCT):*

4.1 For the assessment of the present claims 37 and 38 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4.2 Industrial applicability of the subject-matter of claims 1-36, 39 and 40 is acknowledged.

5. Clarity and support (Art. 6 PCT):

5.1 The subject-matter of claim 38, insofar as it relates to the treatment of NIDDM, anxiety, gastric motility disorders, cancer and cardiovascular disorders is not supported by the description which does not establish an association of ghrelin with any of the said diseases/disorders. Consequently, it appears that a treatment of the said diseases/disorders using an anti-ghrelin antibody would also lack reproducibility (Art. 5 PCT).

5.2 Claims 1 and 2 appear to define the same subject-matter in different terms. One of said claims is therefore superfluous (conciseness).

5.3 The wording of claim 29(a) lacks clarity. It cannot be determined which peptide is used for immunisation. Particular unclear is the formulation "1, 2 or 3 of said contiguous amino acids are selected from amino acids 4, 5 and 6 of human ghrelin". The claim was interpreted as suggesting the immunisation with a peptide having 8, 9, 10, 11, 12, 13, 14, 15, 16 or 17 contiguous amino acids out of amino acid residues 4-20 of human ghrelin.

5.4 Claims 39 and 40 refer to a kit which is considered as being a composition of entities. The claim comprises as an additional feature instructions for using the reagents contained in said kit. Such instructions are characterising a method of using a kit, rather than the kit per se, and as such obscure the scope of the claim since its category is no longer clear (Art. 6 PCT).